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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/523,007

02/01/2005

Neil Goldsmith

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06/04/2010

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EXAMINER

QIAN, CELINE X

ART UNIT

PAPER NUMBER

1636

MAIL DATE

DELIVERY MODE

06/04/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/523,007	Applicant(s) GOLDSMITH ET AL.	
	Examiner CELINE X. QIAN	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 March 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 54, 57-60, 62, 80 and 102-104 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 01 February 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Continuation of Disposition of Claims: Claims pending in the application are 1,2,4,5,7-9,11,15,16,18,23,26,28,30,36,39,43,44,49,54,57-60,62,80 and 102-104.

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DETAILED ACTION

Claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 54, 57-60, 62, 80, 102-104 are pending in the application.

This Office Action is in response to the Amendment filed on 3/15/2010.

Response to Amendment

All rejections of record not reiterated in this Office Action have been withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 54, 57, 59, 60, 62, 80, 102 and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Delcardayre et al., in view of Peterson et al (US 5,783,431).

Delcardayre et al. disclose shuffling methods using artificial chromosome in yeast (see page 62, 3rd paragraph). Delcardayre et al. disclose construction of a YAC library, comprising DNA fragments obtained from a single organism or different individual or species (see bridging paragraph of 62-63). Delcardayre et al. also disclose that individual genes in the library can be linked to yeast regulatory elements to form an expression cassette, and a concatemer of expression cassettes, each containing a different gene, and such concatemers are inserted into YAC (see page 63, lines 5-9). Delcardayre et al. further disclose transforming the YAC library into yeast cells, wherein the cells are induced to undergo meiosis, and then induced to mate,

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following mating, the cells are screened/selected for a desired property (see page 63, 3rd paragraph, and bridging paragraph of 63-64, and 2nd paragraph of page 64). Said process may be repeated until a desired property is acquired (see page 64, 3rd paragraph). Declardyare et al. disclose that each cell may harbor multiple YACs (page 65, line 14), and each YAC may contained two or more selectable marker (for example, a positive marker and a negative marker, see page 62, lines 24-25).

However, Delcardayre et al. do not teach an expression cassette comprising the general formula $[rs_2\text{-}SP\text{-}PR\text{-}X\text{-}TR\text{-}SP\text{-}rs_1]_n$, wherein rs_2 and rs_1 together denote a functional restriction site, SP individually denotes a spacer of at least two nucleotide bases, PR denotes a promoter, capable of functioning in a cell, X denotes an expressible nucleotide sequence, TR denotes a terminator, and $n \geq 2$, and wherein at least a first cassette is different from a second cassette, and substantially all cassette are recognized by the same restriction enzyme, and wherein the expression cassette also comprises an intron between the promoter and the expressible nucleotide sequence.

Peterson et al disclose a method of preparing vectors for expression libraries by linking multiple gene cassettes comprising (5'-3') a promoter, an expressible sequence, and a terminator, see Figs. 5A-5G and columns 47-67. Each cassette comprises, 5' to the promoter, SEQ ID NO: 5 (see column 9, lines 46-64) which comprises the nucleotide sequence 5' GATCTCT 3'. In this case, after *Bgl* *H* digestion, GATC is considered to be rs_2 of the instantly claimed cassette and TCT the 5' spacer. Each cassette from Peterson et al also comprises, 3' to the terminator, SEQ ID NO: 11, which comprises the nucleotide sequence 3' CCCCTAG 5'. In this case, CTAG is considered to be rs_1 of the claimed cassette and CCC the 3' spacer. In this instance, the rs_2 and

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rs1 sequences, together, form the sequence GATC, which is a Mbo I restriction site. The cassettes may differ in their expressible sequences, which may be derived from cDNA or genomic DNA from species as diverse as mammals and bacteria, e.g. as in claim 168 (column 8, lines 20 - 27, columns 17 -19, and Table I). The cassettes may be transformed into, for example, yeast cells (columns 57 - 59), and one such yeast strain may be *S. cerevisiae* (column 21, lines 36 - 37). The number of different library members (i.e. cassettes) may be up to 500,000 (¶ bridging columns 31 - 32) which may be used in concatentation reactions (columns 49 - 50).

It would have been obvious to an ordinary skill in the art to make concatemers comprising the general formula $[rs_2\text{-}SP\text{-}PR\text{-}X\text{-}TR\text{-}SP\text{-}rs_1]_n$ as demonstrated by Peterson et al. and insert into the artificial chromosome to be mixed by mating the host cell and selecting a desired trait based on the teaching of Delcardayre et al. Delcardayre et al. teach the claimed method of mixing heterologous gene in expression cassette located on artificial chromosome, and indicates YACs comprising concatemers of expression cassettes that comprises different combination of genes and regulatory sequences may be used for this method. It would have been obvious to an ordinary artisan to construct the concatemer expression cassettes according to the teaching of Peterson et al. because the advantage of including different combination of genes and recovering said combination of genes is desired in the method taught by Delcardayre et al. It would also have been obvious to an ordinary artisan to varying the number of concatemers to at least 2 copies or 10 copies based on the need because it is contemplated by the teaching of Peterson et al. Combining the prior art methods to achieve the predictable result is within the knowledge of an ordinary skill in the art. Therefore, the claimed invention would have been *prima facie* obvious to the ordinary artisan at the time the invention was made.

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Claim 58 is rejected under 35 U.S.C. 103(a) as being unpatentable over Delcardayre et al., in view of Peterson et al (US 5,783,431) as applied to claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 54, 57, 59, 60, 62, 80, 102 and 104, in further view of Miao et al (US 7,351,813).

The teaching of Delcardayre et al. and Peterson et al. has been described above. However, none of the references teach inclusion of an intron between promoter and the expressible nucleotide sequence.

Miao et al. teach intron may be used in expression cassette. Miao et al. teach that short, functional, intron sequences are preferred in order to keep the size of the expression cassette as small as possible which facilitates the construction and manipulation of the expression cassette. Miao et al. teach the intron can be located at 5' to the coding sequence, 3' to the coding sequence, or within the coding sequence, wherein the advantage of locating the intron 5' to the coding sequence is to minimize the chance of intron interfering with the function of the polyadenylation signal (see col. 7, lines 41-58).

The obviousness of making concatemers comprising the general formula $[rs_2\text{-SP-PR-X-TR-SP-rs}_1]_n$ and insert into the artificial chromosome to be mixed by mating the host cell and selecting a desired trait based on the teaching of Delcardayre et al. and Peterson et al. has been discussed above. The inclusion of an intron in the expression cassette for the desired intonic effect such as splicing in a particular host is routine practice in the art as evidenced by Miao et al., and the teaching of Miao et al. further suggests the advantage of placing the intron 5' to the coding sequence, that is, in between promoter and the coding sequence. Combining the prior art methods to achieve the predictable result is within the knowledge of an ordinary skill in the art.

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Therefore, the claimed invention would have been *prima facie* obvious to the ordinary artisan at the time the invention was made.

Claim 103 is rejected under 35 U.S.C. 103(a) as being unpatentable over Delcardayre et al., in view of Peterson et al (US 5,783,431) as applied to claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 54, 57, 59, 60, 62, 80, 102 and 104, in further view of Smith et al. (PNAS, 1990. Vol.87. pages 8242-8246).

The teaching of Delcardayre et al. and Peterson et al. has been described above. However, none of the references teach inclusion of a conditional centromere in the artificial chromosomes.

Smith et al. teach inclusion of a conditional centromere that can be turned on or off by changing the carbon source in the yeast artificial chromosome (YAC), which allows copy number amplification of the YAC (see abstract).

The obviousness of making concatemers comprising the general formula $[rs_2\text{-SP-PR-X-TR-SP-rs}_1]_n$ and insert into the artificial chromosome to be mixed by mating the host cell and selecting a desired trait based on the teaching of Delcardayre et al. and Peterson et al. has been discussed above. The inclusion of a conditional centromere on YAC is well known in the art for amplifying copy numbers of YAC in the host cell as evidenced by Smith et al. The ordinary artisan would thus recognize the advantage of such centromere and include such centromere on the YAC to of the claimed method for amplifying the copy number in the host cell, which will result in enhancement in screening process. Combining the prior art methods to achieve the predictable result is within the knowledge of an ordinary skill in the art. Therefore, the claimed

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invention would have been *prima facie* obvious to the ordinary artisan at the time the invention was made.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5, 7-9, 11, 15, 16, 18, 23, 26, 28, 30, 36, 39, 43, 44, 49, 52, 54, 56-60, 62, 80, 102-104 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed method using yeast or fungal cells as host, does not reasonably provide enablement for the claimed method in other cell types such as mammalian, vertebrate, plant, insect cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

The nature of the invention:

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The claimed invention is drawn to a method of mixing heterologous genes in expression cassettes located on artificial chromosomes, comprising providing two initial population of cells that can mate with each other, each comprises at least two cells having different combinations of heterologous genes and/or expression cassettes, each cell comprises a first type of artificial chromosome comprising at least two expression cassettes comprising heterologous genes and selectable marker, selecting mated cells that carry at least a subset of the selectable markers presented in the two initial populations.

The breadth of the claim and the teaching of the specification:

The breadth of the claim with regard to the host cell, the initial cell population that comprises artificial chromosomes, in the context of the claimed method is broad. It encompasses any type of cell including eukaryotic cell such as mammalian, vertebrate, invertebrate animals, plants, insect, and prokaryotic cells, etc. However, mixing heterologous expression cassettes located on artificial chromosome through the process of mating do not occur for mammalian, vertebrate, invertebrate, plant and insect cells. For prokaryotic cells such as bacteria, "mating," a process of equal exchange of genetic material or fusing of gametes and creation of a zygote, does not occur. Even if bacterial conjugation is considered "mating," it does not involve meiosis and mixing spores as contemplated by the claimed invention. The specification does not provide guidance for practicing the claimed method in host cells other than yeast or fungal cells. Therefore, the breadth of the claim exceeds the teaching of the specification.

The state of prior art and the predictability in the art:

The state of art at the time of filing does not provide teaching for how to accomplish the mating for the purpose of mixing heterologous gene cassettes located on the artificial

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chromosome and subsequent selection and meiosis in cells other than yeast and fungal species.

In fact, the art teaches that the exchange of genetic material between cells such as mammalian, plant, insect, etc occurs through mechanism other than "mating." As such, whether the claimed method can be practiced with any type of cell is unpredictable. Without teaching from the specification and prior art, one skilled in the art would have to engage in undue experimentation to practice the claimed method to its full scope. Therefore, the claimed invention is only enabled to the scope as indicated above.

Response to Arguments

In response to this rejection, Applicants argue that the disclosure of the specification is sufficient for enablement of the full scope of the invention. Applicants point to the teaching of paragraphs [0035], [0109], [0110], [0039], [0040], [0421]-[0428] for enable the instant method in other types of cell including mammalian cells. Applicants further point to the teaching of paragraph [0112], [0587]-[0589] for teaching mammalian artificial chromosome and human artificial chromosome in application of the claimed method.

The above argument has been fully considered but deemed unpersuasive. The above teaching pointed out by Applicants merely states that possible cell types may be used in the method, and the existence of MAC and HAC, however, they do not teach whether host cell other than yeast and fungus is capable of carrying out the process as claimed. As stated in the previous office action, other types of cell are not known to mate and having spores as claimed in claims 15, 16, 36, etc. As such, the specification does not provide object evidence that the claimed method can be carried out in cell other than yeast and fungus, with either mating or cell fusion

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process. Therefore, for reason set forth in the previous office action and above, this rejection is maintained.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELINE X. QIAN whose telephone number is (571)272-0777. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Celine X Qian /
Primary Examiner, Art Unit 1636

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